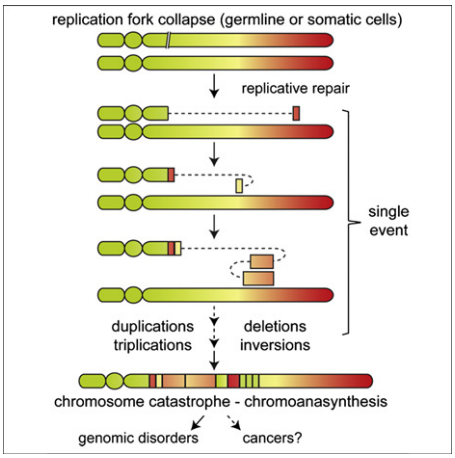
In This Issue

Cell



Chromothripsis Moves beyond Cancer

PAGE 889

Chromothripsis, a phenomenon in which numerous genomic rearrangements are apparently acquired in one single catastrophic event, has been characterized in cancer genomes. Liu et al. now document that patients with developmental disorders also harbor complex genomic rearrangements with features of chromothripsis. The authors provide evidence that these germline-acquired chromosome catastrophes occur through DNA replication errors rather than the shattering and reassembly of a chromosome.

Blocking Myc in Myeloma

PAGE 904

Despite the centrality of Myc in the pathogenesis of cancer, conventional approaches for direct Myc inhibition have not proven successful. By targeting chromatin regulatory complexes influencing Myc expression with a chemical probe of BET bromodomains, Delmore et al. block *MYC* transcription and demonstrate the efficacy of this compound in mouse models of multiple myeloma.

Positive ID on a Tumor Target

PAGE 918

ID proteins inhibit differentiation and maintain stem cell fate and are ubiquitinated and degraded in differentiated tissues. However, in many neoplasms, IDs appear to escape degradation. Williams et al. now identify USP1 as the deubiquitinating enzyme controlling ID protein stability and show that, by promoting ID stability, USP1 preserves stem cell-like characteristics of osteosarcoma tumor cells. Their findings suggest that the USP1-ID axis that normally controls bone development is usurped to propagate osteosarcoma tumor stem cells and point to USP1 as an attractive target for differentiation therapy.

Helicase Merges onto the Single-Stranded Highway

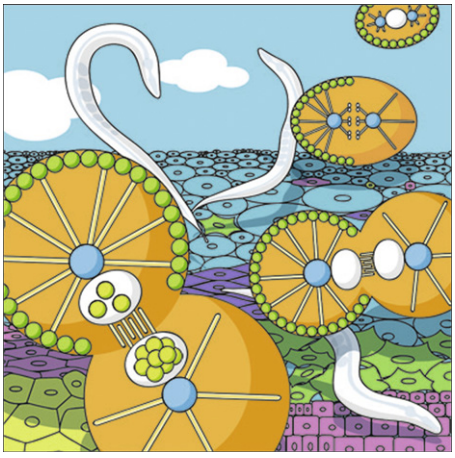
PAGE 931

The eukaryotic replicative helicase complex CMG is loaded onto dsDNA, but it could, in principle, unwind DNA by translocating along ssDNA or dsDNA. By colliding replisomes with strand-specific roadblocks in Xenopus egg extracts, Fu et al. show that CMG can bypass a lagging strand, but not a leading strand roadblock, strongly supporting a 3'-to-5' ssDNA translocation mechanism. Replication initiation therefore likely involves reconfiguration from a dsDNA to an ssDNA binding mode.

Microtubules Master Transcription

PAGE 942

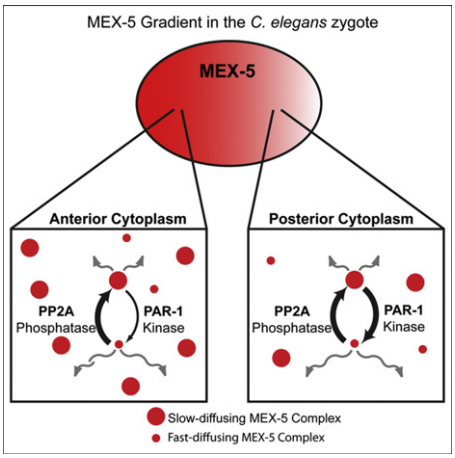
Sugioka et al. show that extrinsic signals that remodel the cytoskeleton lead to asymmetric gene expression and cell fate in the dividing *C. elegans* embryo. Wnt signaling generates an asymmetry in the astral microtubules that, in turn, influences the levels of β-catenin in the nuclei of daughter cells as they separate from each other. The findings point to a direct role of cytoskeletal dynamics in transcriptional regulation.



Acetylation Winds the Aging Clock

PAGE 969

Lu et al. find that yeast lifespan is regulated by an intrinsic timing mechanism that acts in parallel with nutrient-sensitive aging pathways. Acetylation of a subunit of AMPK decreases with age, leading to the progressive phosphorylation of Akt. The energy sensor AMPK therefore acts in a nutrient-independent manner to regulate longevity.



A New Recipe for Making Gradients

PAGE 955

Griffin et al. show that the MEX-5 protein gradient in the *C. elegans* zygote arises from a localized phosphorylation/dephosphorylation cycle that regulates the rate of MEX-5 diffusion. These results present a paradigm for protein concentration gradient formation that does not require localized protein synthesis or degradation.

Endothelium at the Eye of the Storm

PAGE 980

Cytokine storms are excessive and potentially fatal immune responses to influenza and other viral infections. Teijaro et al. find that activation of the sphingosine-1-phosphate receptor ($S1P_1$) suppresses early immune responses, preventing cytokine storms and protecting mice from pathogenic human influenza virus. S1P1 is expressed in vascular endothelial cells in the lung, identifying these cells as key mediators of the response to influenza infections and suggesting a potential therapeutic path for preventing morbidity due to cytokine storms.

Toggling Hunger

PAGE 992

How is hunger neuronally coded? Using a combination of optogenetic, electrophysiological, and pharmacological approaches, Yang et al. demonstrate that hunger or an appetite-stimulating hormone induces synaptic activity in the neurons that drive feeding behavior. This activity persists due to a positive feedback loop involving AMPK and neuronal calcium release until leptin, a hormone signaling satiety, switches it off. The findings reveal a neuronal circuit, switched on and off by hormonal pulses, that operates as a memory storage device for a physiological state.

A Neuron in Any Other Place Would Smell as Sweet

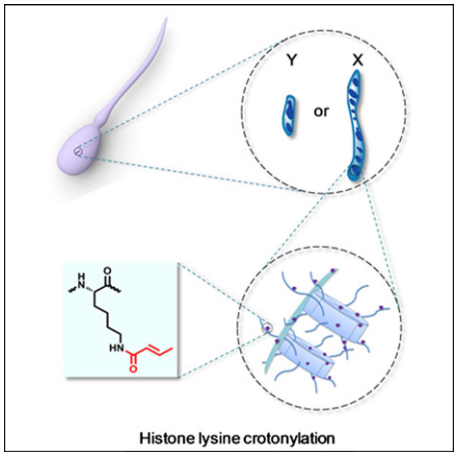
PAGE 1004

Choi et al. probe how the brain translates sensory stimulation such as odors to behavior. By artificially stimulating clusters of neurons in a region where olfactory information is processed (the piriform cortex), the authors show that activating the same arbitrarily chosen neuronal cluster can lead to opposite behavioral responses, depending on the experience (aversive or attractive) coupled to the neuronal stimulation. The findings highlight the plasticity of responses to olfactory stimuli and indicate that spatial order in the piriform does not inform odorant identity or behavioral output.

Histone Vocabulary Explodes

PAGE 1016

The diversity of histone modifications and their many functions becomes ever more complex. Tan et al. now identify 67 histone marks, including lysine crotonylation. This modification is evolutionarily conserved, abundant in core histones, and marks either active promoters or potential enhancers. Their data also suggest that lysine crotonlyation marks active sex chromosome genes in male germ cells.



Going Ape Over the Sperm Methylome

PAGE 1029

Genome-wide reference maps of DNA methylation are critical to an understanding of its many roles in gene regulation. Molaro et al. generate full DNA methylation profiles of human and chimp sperm and compare these to embryonic stem cells. Their findings reveal distinct properties for the epigenetic reprogramming that occurs in germ cells and somatic cells during mammalian development and provide insight into the relationships between the evolution of the genome and the epigenome.